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RELATED PCT APPLICATION NUMBER: *PCT/US04/43595*

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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION Under 37 CFR 1.53 (b)(2).

Attorney Docket No.	585.P	Type a plus sign (+) inside this box -----> +

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TITLE OF THE INVENTION (280 characters max)

Phosphonate Prodrugs of CP-690,550

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ENCLOSED APPLICATION PARTS (check all that apply)

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[ ] Small Entity Statement
[ ] Drawing(s) — *Number of sheets* ____
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[X] The Commissioner is hereby authorized to charge filing fees (as well as any additional fees which may be required by this paper) and credit Deposit Account Number **07-1250**. Provisional Filing Fee Amount ($) **$160.00**

The invention was made by an agency of the United States Government of under a contract with an agency of the United States Government.

[X] No.
[ ] Yes, the name of the U.S. Government Agency and the Government contract number are:

Respectfully submitted,

SIGNATURE _____ DATE December 22, 2003

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[ ] Additional inventors are being named on separately numbered sheets attached hereto

PATENT

Attorney Docket No. 585.P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Carina E. Cannizzaro, James M. Chen, Aesop Cho, Lee S. Chong, Manoj C. Desai, Maria Fardis, Sundaramoorthi Swaminathan and William J. Watkins

For: Phosphonate Prodrugs of CP-690,550

Mail Stop Provisional Patent Application
Commissioner for Patents
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PROVISIONAL APPLICATION COVER SHEET
(37 C.F.R. § 1.51 (2) (i))

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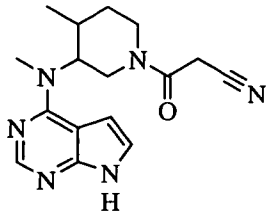
Phosphonate Prodrugs of CP-690,550

CP-690,550 (WO 02,096,909, structure below) is an orally available Janus kinase (JAK)-3 inhibitor, for the potential treatment of transplant rejection and psoriasis.

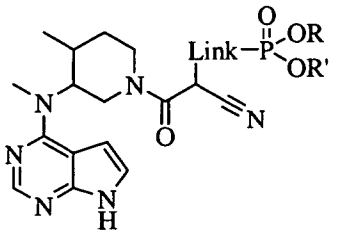


CP-690,550

In spite of numerous treatment options for organ transplant and autoimmune disease patients, there remains a need for effective and safe immunosuppressive agents. The most significant complications of drugs used for transplant patients include nephrotoxicity, neurotoxicity, new-onset posttransplant diabetes mellitus, hyperlipidemia, and hypertention. In this respect, a molecular target restricted in expression to immune cells could provide immunosuppressive efficacy without the toxicity associated with current therapies. Cytokine receptors are critical for the development and homeostasis of immune cells. These receptors all require the cytoplasmic tyrosine kinase JAK3 for signaling (Changelian, P. S. *et al.*, *Science*, **2003**, *302*, 875). Therefore, reduction of the dose and/or improvement of efficacy might be achieved by the use of pro-drugs of

analogs of CP-690,550 that, upon cleavage inside the target cell, give rise to agents with increased intracellular half-lives. Such phosphonate pro-drug compounds are described below.

Figure 1:



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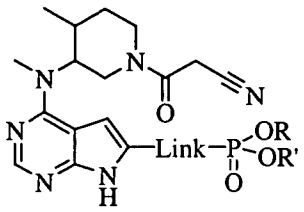
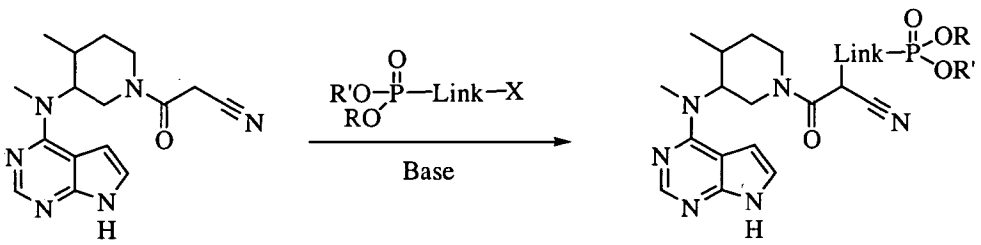


2

Link is 0-8 atoms, with 2-6 preferred

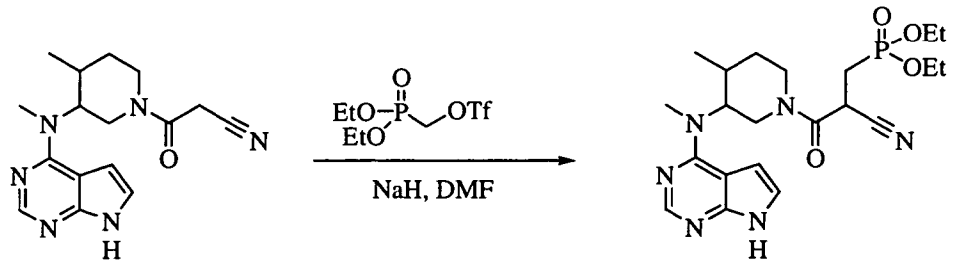
Compounds such as **1** can be made according to the general route outlined in Scheme 1, with an example depicted in Scheme 2.

Scheme 1:



1

Scheme 2:

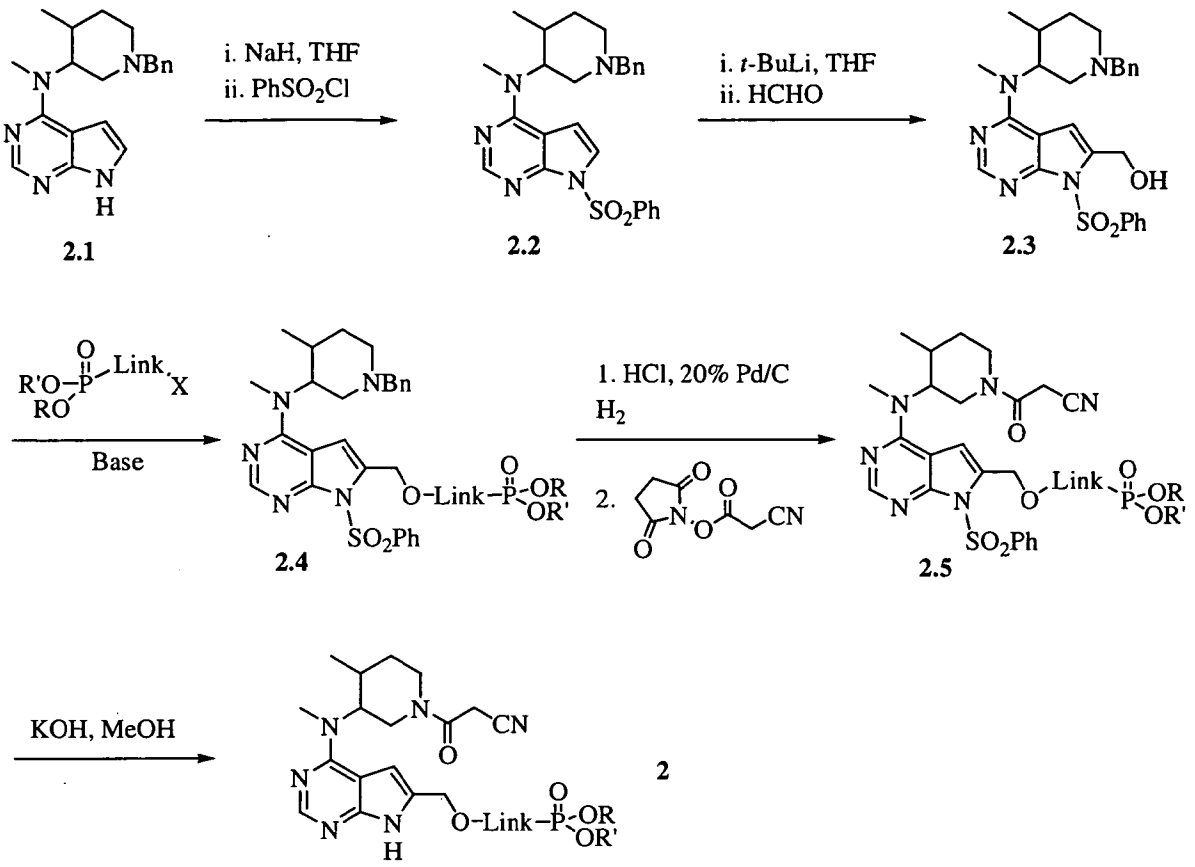


1

CP-690,550, 3-{4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile, can be prepared as described in WO 02,096,909 and WO 03,048,162. Enolate formation at the α-cyanoamide position using over 2 equivalents of base followed by addition of diethyl phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, **1986**, *27*, 1477) yields the desired compound **1** shown in Scheme 1. A solvent such as THF, DMF or other anhydrous solvents may be used for this reaction. In case the pyrrole nitrogen interferes with the desired alkylation, a protecting group such as BOC may be introduced before the alkylation reaction. Removal of the BOC group can be accomplished by exposure of the reaction product to TFA as described in Greene, T., Protective groups in organic synthesis, Wiley-Interscience, 1999.

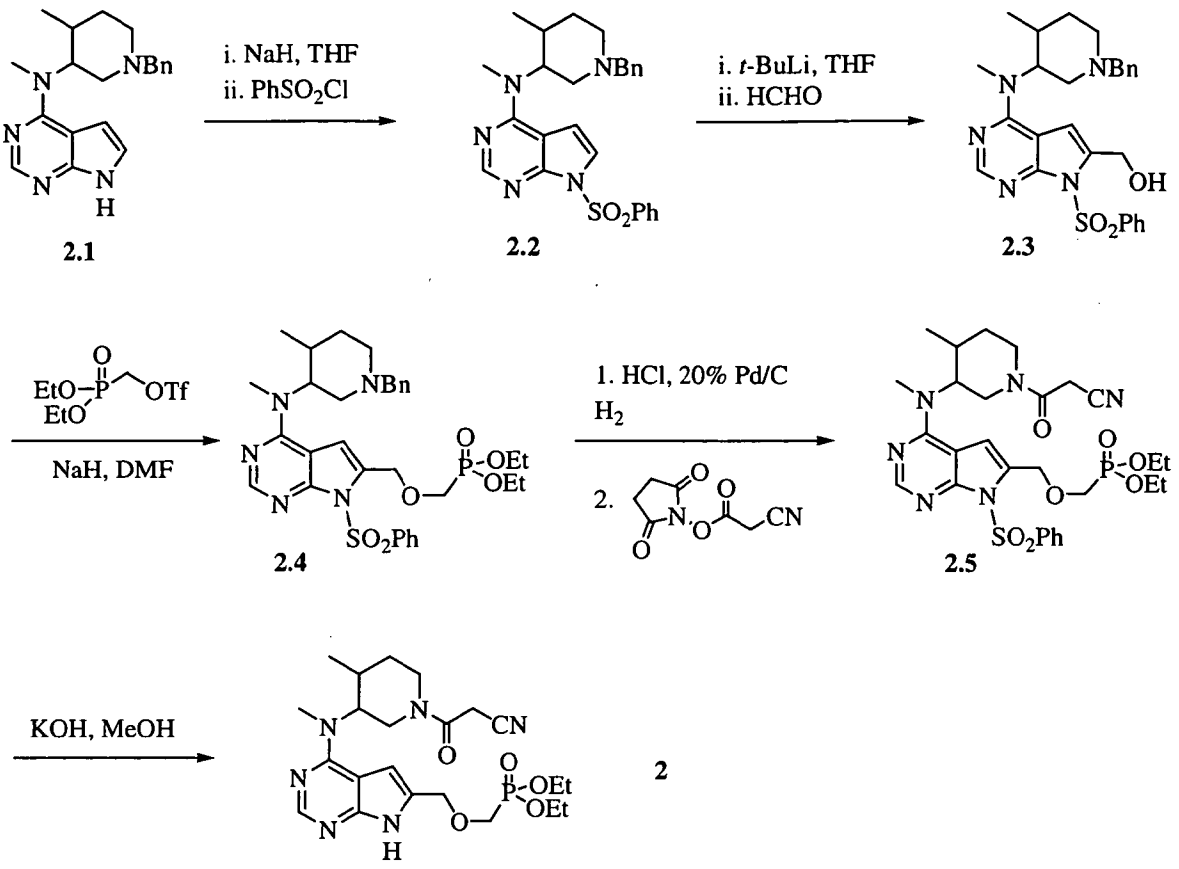
A second series of pro-drugs can be prepared by attaching the phosphonate group on to the pyrrole ring at the 2-position. Compounds such as **2** can be made according to the general route outlined in Scheme 3, with an example depicted in Scheme 4.

Scheme 3:



Compound **2.1** is prepared according to WO 02,096,909. Protection of the pyrrole nitrogen using a tosyl group is achieved as described in Sakamoto, T. *et al., Tetrahedron Lett.* **1994**, *35*, 18, 2919. Ortho lithiation using *t*-BuLi and quenching with formaldehyde as described in the above reference as well as Seela, F. *et al., Chem. Ber.* **1977**, *110*, 4, 1462 introduces a substituent at the requisite site. The primary alcohol so formed may be used for attachment of the phosphonate moiety via ether formation using base and diethyl phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, **1986**, *27*, 1477) in an anhydrous solvent. Removal of the benzyl protecting group is achieved using hydrogenolysis conditions. The piperidine nitrogen is then coupled with cyano-acetic acid 2,5-dioxo-pyrrolidine-1-yl ester to provide compound **2.5**. Removal of the tosyl protecting group can be achieved using basic conditions to provide the desired product **2**.

Scheme 4:



Specifically, (1-benzyl-4-methyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine, compound **2.1** (prepared as described in WO 02,096,909) is first protected on the pyrrole nitrogen using a tosyl group. Subsequent formylation using the procedure reported by Sakamoto, T. *et al.,* (*Tetrahedron Lett.* **1994**, *35*, 2919) provides compound **2.3**. The primary alcohol is then treated in a solvent such as tetrahydrofuran or dimethylformamide with a base such as sodium hydride. When bubbling ceases, diethyl phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, **1986**, *27*, 1477) is added, yielding the desired product **2.4**. Debenzylation of the piperidine nitrogen following by coupling to cyano-acetic acid 2,5-dioxo-pyrrolidine-1-yl ester gives compound **2.5**. Removal of the tosyl protecting group provides the desired pro-drug **2**.

Interconversions of the phosphonates between R-link-P(O)(OR^1)$_2$, R-link-P(O)(OR^1)(OH), R-link-P(O)(OR^1)(OR^2) and R-link-P(O)(OH)$_2$.

The interconversion reactions of phosphonates are illustrated in Scheme A. The interconversions may be carried out in the precursor compounds or the final products

using the methods described below. The methods employed for a given phosphonate transformation depend on the nature of the substituents R^1, R^2. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester A.1 into the corresponding phosphonate monoester A.2 (Scheme A, Reaction 1) can be accomplished by a number of methods. For example, the ester A.1 in which R^1 is an aralkyl group such as benzyl, can be converted into the monoester compound A.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in *J. Org. Chem.*, **1995**, *60*, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester A.1 in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester A.2 can be effected by treatment of the ester A.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters A.1 in which one of the groups R^1 is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters A.2 in which R^2 is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters A.1 in which one or both of the groups R^1, R^2 is (2-trimethylsilyl)ethyl can be converted into the monoesters A.2 by treatment with a fluoride source such as tetrabutylammonuium fluoride in a solvent such as tetrahydrofuran. Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, can be converted into the monoester A.2 in which R^2 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in *J. Org. Chem.*, **1973**, *38* 3224 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester A.1 or a phosphonate monoester A.2 into the corresponding phosphonic acid A.3 (Scheme A, Reactions 2 and 3) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in *J. Chem. Soc., Chem. Comm.*, **1979**, 739. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as

bis(trimethylsilyl)trifluoroacetamide or a base such as 2,6-lutidine, at ambient temperature. Phosphonate diesters A.1 in which both of the groups R^1, R^2 are (2-trimethylsilyl)ethyl can be converted into the corresponding phosphonic acid A.3 by treatment with a strong acid such as trifluoroacetic acid (*Tet. Letts.*, **1993**, *34*, 3377). A phosphonate monoester A.2 in which R^1 is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid A.3 by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester A.2 in which R^1 is alkenyl such as, for example, allyl, can be converted into the phosphonic acid A.3 by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, **1985**, *68*, 618. Palladium-catalyzed hydrogenolysis of phosphonate esters A.1 in which R^1 is benzyl is described in *J. Org. Chem.*, **1959**, *24*, 434. Platinum-catalyzed hydrogenolysis of phosphonate esters A.1 in which R^1 is phenyl is described in *J. Amer. Chem. Soc.*, **1956**, *78*, 2336.

The conversion of a phosphonate monoester A.2 into a phosphonate diester A.1 (Scheme A, Reaction 4) in which the newly introduced R^2 group is alkyl, aralkyl, haloalkyl such as chloroethyl, silylethyl such as 2-trimethylsilylethyl or aralkyl can be effected by a number of reactions in which the substrate A.2 is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triarylphosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester A.2 to the diester A.1 can be effected by the use of the Mitsunobu reaction (*Bull. Chem. Soc. Japan.*, **1971**, *44*, 3427). The substrate is reacted with the hydroxy compound R^1OH, in the presence of a dialkyl azodicarboxylate such as diethyl azodicarboxylate and a triarylphosphine such as triphenylphosphine. Alternatively, the phosphonate monoester

A.2 can be transformed into the phosphonate diester A.1, in which the introduced R^2 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^2Br, in which R^2 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester A.2 is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^2OH, in the presence of a base such as triethylamine, to afford the phosphonate diester A.1.

A phosphonic acid R-link-$P(O)(OH)_2$ can be transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme A, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester R-link-$P(O)(OR^1)_2$ A.1, except that only one molar proportion of the component R^1OH or R^1Br is employed.

A phosphonic acid R-link-$P(O)(OH)_2$ A.3 can be transformed into a phosphonate diester R-link-$P(O)(OR^1)_2$ A.1 (Scheme A, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids A.3 can be transformed into phosphonic esters A.1 in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°C. Alternatively, phosphonic acids A.3 can be transformed into phosphonate diesters A.1 in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonate diester A.1.

Scheme A